Delivering Precision Medicine in Oncology Today and in Future-The Promise and Challenges of Personalised Cancer Medicine: a position paper by the European Society for Medical Oncology (ESMO)

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Key Message: "A new era of personalised cancer medicine will touch every aspect of cancer care—from patient counselling, to cancer diagnosis, tumour classification, treatment and outcome—that demands a new level of in-depth education and collaboration between researchers, cancer specialists, patients and other stakeholders. In this position paper, ESMO sets out the current status in the field of personalised cancer medicine and addresses issues and challenges for the medical oncology community."

Abstract

Although the description and interpretation of cancer genetics has been at the core of cancer research for more than a century, in this decade genomic medicine is set to profoundly transform every aspect of cancer care. Already, the anecdotal cases of individuals who have not responded to conventional chemotherapy but for whom whole genome sequencing has identified a gene target for directed therapy with remarkable clinical effect [1], point to a time in the not-too-distant future when cancer genome sequencing will be a routine adjunct to the clinico-pathological 'work-up' of a newly diagnosed cancer. For now, the identification of genes central to cancer biology is generating highly relevant diagnostic, prognostic and therapeutic information that has already translated to the clinic. The extraordinary pace of change is set to continue. The new era of personalised cancer medicine will touch every aspect of cancer care—from patient counselling, to cancer diagnosis, tumour classification, treatment and outcome—that demands a new level of in-depth education and collaboration between researchers, cancer specialists, patients and other stakeholders. In this position paper, ESMO sets out the current status in the field of personalised cancer medicine and addresses issues and challenges for the medical oncology community.

Key words: precision medicine, personalised medicine, cancer, medical oncology

Defining Personalised Cancer Medicine

In its broadest sense, 'personalised medicine' is the tailoring of medical treatment to the characteristics of an individual patient and moves beyond the current approach of stratifying patients into treatment groups based on phenotypic biomarkers. Nowhere in medicine has the impact of personalised medicine been greater than in oncology. For scientists and oncologists, the term 'personalised medicine' is often used interchangeably with terms such as 'genomic medicine', 'precision medicine' and 'precision oncology'. These terms are used to describe the use of an individual patient's molecular information (including genomics and proteomics) to inform diagnosis, prognosis, treatment and prevention of cancer for that patient. As the transition from stratified cancer medicine to truly personalised cancer medicine intensifies, it is this definition that the ESMO Personalised Medicine Task Force prefers to use when describing personalised cancer medicine. But irrespective of the term used, the direction of travel is clear—precision diagnosis and treatment of cancer at the molecular level—and this change in paradigm has profound implications, from preclinical definition of mechanism of action to the development of molecular taxonomies of cancer, and from genome diagnostics to trial design.

From Genomics to Clinics—the Context and History of Personalised Medicine

Although much of cancer biology is based on the central tenet that it is a genetic disease, caused by a clone of cells that expands in an unregulated fashion because of somatically-acquired mutations, this view contributed little to cancer treatment until the 21st century. The targeting of *HER2* overexpression with the monoclonal antibody, trastuzumab, to improve outcome in metastatic breast cancer was the first example of targeted treatment [2]; but the paradigm of targeted interference of an oncogene with a specifically designed small molecular inhibitor is best exemplified by imatinib. The tyrosine kinase inhibitor imatinib, developed to target the *BCR-ABL* fusion gene, a consequence of the Philadelphia chromosome and pathognomonic of chronic myeloid leukaemia, transformed the care of patients, changing this aggressive, life-threatening disease to a manageable chronic disease [3]. Around the same time, the initiation of the Cancer Genome Project at the Wellcome Trust's Sanger Institute using exon Sanger sequencing quickly identified somatic mutations in the *BRAF* gene in the majority of malignant melanoma [4]. This opened a window into the biology of these tumours and provided the starting point for successful clinical translation, with the development of vemurafenib that specifically targets the underlying molecular lesion [5].

With the launch of large-scale cancer whole genome sequencing (WGS) projects such as the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA) expected to deliver a complete catalogue of genomic alterations in primary cancers and begin to elucidate the mutational patterns and influences across the natural history of cancers [6, 7], connecting recurrent genomic alterations to altered pathways and acquired cellular vulnerabilities will open the door to targeted therapies [7]. At the same time, elucidation of the mechanisms underlying the processes generating somatic mutations will lead to new insights into cancer causation and, potentially, new approaches to prevention [8].

Oncology – At the Frontline of Utilising Personalised Medicine

Oncology is at the frontline of personalised medicine, moving beyond the previous model of giving cancer therapeutics based on trials of largely unselected patients beyond a simple phenotypic marker, to leading the way in utilising the molecular profile of an individual's cancer genome to optimise their disease management. At the centre is the patient, with personalised medicine offering the promise of delivering safe and efficacious cancer treatments that are targeted, biologically rational, and avoid over- and under-treatment common with traditional chemotherapy, thus reducing toxicities associated with non-specific modes of action of chemotherapy. An intriguing example is the characterisation of germline variations in cancer patients that predict anthracycline-related cardiomyopathy and cisplatin-associated ototoxicity and now provide a mechanism for prospective identification of at-risk patients [9, 10].

The experiences of the oncology community in developing and delivering precision medicine are not unique and have parallels, more broadly, in other areas of medicine. For example, the progress made in cystic fibrosis (CF) in developing treatments to correct the basic CF transmembrane conductance regulator (CFTR) protein has profoundly changed CF in a way that closely mirrors oncology, in particular the development of the novel drug, ivacaftor for molecularly-distinct sub-types of CF when the mutational class is confirmed by companion diagnostic testing [11]. In addition, genomic sequencing is transforming the diagnosis of children with unclassified Mendelian defects although with limited therapeutic implications for the moment [12]. Looking beyond a 5-year horizon, pharmaceutical company pipelines show a preponderance of drugs that have companion diagnostics for therapy selection in immunology and central nervous system disease. Assessing additional factors that include the relative economics of personalised medicine, it has been suggested that it is these disease classes, and those involving anti-infectives and cardiovascular disease that will hold the greatest potential to improve treatment through personalised medicine [13].

Delivering Personalised Cancer Medicine: Challenges and Promise

This simply stated goal—the tailoring of medical treatment to the individual characteristics of a cancer patient—hides much complexity and there are considerable challenges to be addressed. At a broad level, the introduction of WGS to guide healthcare decisions presents immense challenges to clinical practice as we know it, notwithstanding the technical cost of generating the sequence. For the patient with cancer, major factors to consider include tumour heterogeneity, technical feasibility and validity of biomarkers, the daunting task of integrating and interpreting the ever-increasing volume of data and the associated information communication technology (ICT) needs, and the multiple dimensions of, and changing perspectives on, value and cost effectiveness in personalised cancer medicine.

Tumour heterogeneity, molecular evolution and drug resistance

Tumours exhibit extensive heterogeneity, both between and within tumours, driving phenotypic variation and posing a significant challenge to personalised cancer medicine [14]. The extensive heterogeneity of common cancers, seen in the expression of protein biomarkers, and at multiple genetic and epigenetic levels, complicates our understanding of cancer pathways and potentially confounds biomarker validation through tumour sampling bias. But it is the clonal make-up of tumours, their molecular evolution and their relationship with drug response and resistance that carries perhaps the greatest challenge to pursuing personalised cancer medicine. Most recently, it is becoming clearer that classical views of clonal architecture in tumours, previously characterised as a driver mutation followed by a linear accumulation of additional mutational insults, is too simplistic and that there is huge variation in the genetic profile of an individual tumour. Analysis of a series of renal cell carcinomas found two clonally-dominant founder events in all samples across the tumours, but revealed myriad subclones that carried distinct genetic profiles within each tumour [15]. It is this intra-tumour heterogeneity and subclone diversity that likely contributes to treatment resistance. This branched 'Darwinian-like' evolution of tumours represents a significant challenge but also may offer insights into more refined and personalised therapeutic targeting. Identification of driver events at the evolutionary trunk of a tumour and understanding the evolutionary changes of a tumour during treatment and progression may identify targets of resistance or progression. Understanding the nature and mechanism of these genomic events may also identify an 'Achilles heel' that could be exploited therapeutically [16-19], for example through the targeting of additional genetic mutations contained within recognised high-risk subclones.

A tumour, therefore, may not comprise of a single dominant clone but contain multiple co-existing sub-clones with the implication that these can be spatially separated or intermixed within the same biopsy. Furthermore, heterogeneity exists over the lifetime of a cancer, with differing patterns of genetic changes from initiation through to metastasis and relapse after surgery or therapy [18]. Longitudinal tumour sampling approaches will be essential to decipher the impact of tumour heterogeneity on cancer evolution, and this will necessitate the development of minimally invasive methods to profile tumour genomes. The ongoing TRACERx (Tracking Cancer Evolution through Therapy) study [20] in lung cancer is utilising both biopsy and blood samples (for circulating DNA) taken throughout the course of the disease [21]. Intratumoural heterogeneity represents a significant clinical problem as a single biopsy may not be representative of the genetic composition of the cancer and a single snap-shot biopsy at a single time-point may no longer be sufficient. Alternative approaches, such as utilising and validating more accessible material such as formalin-fixed, paraffin-embedded tissue, circulating tumour cells, protein or DNA, and molecular imaging may contribute.

Clinical management that recognises the evolving nature of the tumour genome will be necessary to improve patient outcome. For now, ESMO recognises that these entwined difficulties of tumour heterogeneity, clonal evolution and invasive biopsy remain substantive issues and research priorities [19].

Precision diagnostics and predictive biomarkers of therapeutic response

Both the mutation profile of a tumour, and germline mutations—heritable aberrations found within the individual—may influence disease outcome and/or response to therapy. These cancer biomarkers can be broadly classified as prognostic markers—those mainly associated with the course or outcome of a disease—or predictive markers, which can be used to identify subpopulations of patients who are most likely to respond to a given therapy [9]. More recently, pharmacodynamic biomarkers are beginning to support decisions around drug target validation and dosage.

The promise of biomarkers is having a tremendous impact on cancer medicine. In the United States, there are now 85 companion diagnostics and more than 500 clinically relevant biomarkers in drug labels [22]. A large number of drugs in clinical development are associated with a biomarker, and the inclusion of biomarkers in clinical trials requires a number of design and regulatory issues to be

resolved. These include the positive/negative cut-off for biomarkers without a dichotomous outcome (e.g. expression levels) and the choice of assay and validated laboratory test to record the biomarker, critically important decisions that define the study population and contribute to the utility of the test once the biomarker/drug treatment combination has been proven effective and safe. The European Medicines Agency (EMA) guideline on anticancer drug evaluation recommends the development of biomarker diagnostic methods early in clinical development, and specifies that a diagnostic assay complying with the regulatory requirements is available at time of licensure [23].

Availability of, and access to, biological material that is of suitable quality is critical; trial protocols may mandate the collection and analysis of biological samples pre-, post- and during treatment. This is recognised in the EMA guidelines, and raises ethical and legal issues, procedural risks and the need for patient education and consent [23]. ESMO advocates 'broad patient consent' at the outset of patient participation, allowing for additional studies to be undertaken without the need for ongoing re-consent. In commercial clinical trials, clinical research organisations are increasingly offering biomaterial collection and storage and biobanks are also driving the standards of storage [13].

As more biomarkers become clinically actionable, multiple single tests become unfeasible and the move away from the single-diagnostic/single-drug paradigm is likely to accelerate. Full molecular characterisation to drive appropriate, targeted combinations of therapies to account for multiple drivers of tumour progression and mechanisms of resistance are likely future steps. The development of multi-gene assays could overcome some of these problems but in the longer term next generation sequencing technologies may provide a solution to the methodological and technical demands of cancer diagnostics [24]. As these platforms evolve, they will provide robust tools for molecular diagnostics only when paired with robust interpretive frameworks that allow biomarker/genomic data correlates with clinical efficacy and safety. Although a major challenge will be to integrate and make biologic sense of the massive amount of data derived from multiple platforms, it is likely that concomitant developments in computational science will enable automation of much of the analytical and interpretative processes.

Whatever technology emerges, biomarkers need to be validated, standardised, reproducible and delivered in a timeframe that is compliant with good clinical care. Clinical laboratory certification and external quality assurance (EQA) programmes are essential to guarantee optimal quality of testing and maintenance of intra- and inter-laboratory consistency [25]. There are several EQA programme schemes available across Europe but these vary in their scope and size. ESMO representatives are working in partnership with a number of other European stakeholders to derive

a consensus set of guidelines for EQA to help improve the quality of tumour molecular pathology [25].

As the evidence base expands and more biomarkers are linked to a targeted drug response, there will be a temptation to link each tumour possessing a particular biomarker to a targeted therapy and prescribe accordingly, despite a lack of validation or integration into medical decision making. ESMO recognises the importance of large, collaborative, translational research projects that aim to link clinical, demographic, and outcome data to histology and molecular profiles to enhance the clinical application of these data within a rigorous evidence framework. Collaborative international programmes already in place include AURORA [26], developed by the Breast International Group (BIG), Lungscape [27], run by the European Thoracic Oncology Platform (ETOP) and SPECTAcolor [28]—the first pan-European Biomarker Screening Platform dedicated to patients with advanced colorectal cancer—created by the European Organisation for Research and Treatment of Cancer (EORTC).

Large scale data disclosure from all players in the personalised cancer medicine field, including pharmaceutical companies, to create an 'open source' molecular medicine global knowledge network, would likely drive further innovation in this field [23]. While this may bring benefits for scientific research and patient care, open source data, particularly if participant-level data, may bring unintended consequences and therefore should be pursued with caution so that potential risks to participants and trial sponsors are addressed without blocking the progress and promise that open source data can bring [29].

A new discipline of healthcare knowledge engineering?

As cancer treatment evolves from stratified to personalised cancer medicine, there remain major challenges in ICT and bioinformatics. Large scale genomic data will need to be integrated with clinical data, analysed and translated into information to serve as guidance for clinical decisions. Furthermore the vast amount of information generated from translational research initiatives and 'big science' projects, like the cancer genome projects, need to be translated and interpreted, with effective information flow between laboratory and clinical researchers a prerequisite [30]. Despite present concerns about this complexity, automation of much of the analytical and interpretive processes is likely to develop alongside the genomic technologies and drive understanding to a new

level. However, this suggests a new focus on healthcare knowledge engineering is needed to facilitate this knowledge transmission across the research–healthcare gap [30].

Engaging, protecting and communicating with patients

It is likely large-scale whole genome sequencing will be increasingly utilised for selecting patients for specific therapy. This raises a number of ethical concerns in areas beyond cancer care provision. Genomic sequencing has the potential to reveal increased risk for cancer syndromes, as well as other diseases and this raises issues of privacy, data protection and discrimination. In such cases, reporting the results could be clinically meaningful and/or life-saving. Disclosure of results from genetic testing that are clinically and analytically valid can be positive, helping patients take control of their lives. For example, individuals with BRCA1/2 mutations can benefit from prophylactic surgery to prevent cancer or from surveillance to detect cancers early. Providing feedback opportunities might also contribute to involving and educating patients and patients' advocacy groups and there is wide public interest in being informed of such results [31]. Nonetheless, there is not enough research studying cancer patients' preferences and expectations concerning genetic testing [31]. Continuing research and discussions to develop ethical and legal frameworks and establish counselling recommendations on disclosing information from genetic testing to cancer patients and their relatives are required. Furthermore, patients' involvement in this process will be essential to further improve the translation of genetic testing data to the benefit of cancer patients.

Capturing value in personalised cancer medicine

Personalised cancer medicine has the potential to improve health outcomes and cost-effectiveness in a healthcare system but the actual economic assessment of this treatment approach is fraught with challenges. In theory, personalised cancer medicine is promising from an economic perspective because in principle only those patients who are likely to benefit receive treatment and this avoids treating patients with potentially toxic therapy for which there is no clinical benefit. Biologically designed, early-phase clinical trials in a subset of patients may also avoid costly phase III trials that fail to deliver. If the oncogenic driver is identified, and a companion diagnostic available and validated pre-clinically for a highly selective therapy, proof-of-concept trials can be anticipated very early in the clinical development of the therapy [32].

The current cost-effective analysis framework of using health gain to describe the value of complex health technology such as personalised cancer medicine is not likely to sufficiently capture all its benefits [33]. Appropriate health outcome models for personalised cancer medicine are required. In

Europe, the majority of patients have healthcare access provided through nationally funded programmes, although the resources of these vary widely, which imposes certain limitations on the availability of stratified oncology and the future of personalised cancer medicine. Even in well-funded systems, access to newer therapies and the accompanying companion diagnostic is often restricted, as agent pricing often exceeds the 'cost-effectiveness thresholds' used to approve new treatments. Often the highest value is attributed to the treatment rather than the diagnostic. Furthermore, separate regulatory pathways for drug and diagnostic approval exist in Europe and between funding streams for targeted treatment and the accompanying companion diagnostic.

Medical insurance companies also place restrictions on such treatments, and currently in Europe the cost of the accompanying companion diagnostic is not supported by third party payers [34]. These aspects each contribute to potential and indeed actual imbalances in access, which, under present systems, can only increase as the identification of novel targets and treatments continues.

Economic modelling of upfront *KRAS* testing in patients with metastatic colorectal cancer suggested cost savings could be made and spare patients from ineffective and toxic therapies [35]. More recently a cost effective analysis of the targeted treatment crizotinib for ALK-positive NSCLC showed this was not cost effective because of the low frequency of the marker in the population and the high cost of the drug [36]. In the UK, the National Institute for Health and Care Excellence (NICE) declined funding of crizotinib, and while deemed clinically effective could not be considered cost effective. The example of the French National Cancer Institute (INCa) offers an important model, in which nationally funded molecular diagnostics of cancer is realising savings to the health insurance system as a whole through targeted drugs coupled with companion diagnostics [37]. A disease-specific economic model for breast cancer showed that a 37% reduction in total treatment costs could be realised without affecting the average quality-adjusted life years (QALY) by early stratification of women based on age, history and genetic profile, although these savings would only be realised if the infrastructure for diagnostics and electronic health records was in place [38].

As the cost of whole genome sequencing continues to fall, the costs of education and training, infrastructure and implementation of new clinical treatment pathways needs to considered. The cost of any new drug is important and needs to be balanced between supporting innovation and investment with what an individual or health care system can afford. Organisations such as the Health Economic Policy and Reimbursement Committee within the European Personalised Medicine Association [39] and the Personalised Medicine coalition [40] have provided recommendations to address the delivery of personalised medicine across Europe and produced working documents which summarise the need to re-evaluate existing assessment and payment systems.

More evidence is needed to support the notion that personalised cancer medicine can increase healthcare quality and improve patient outcome while lowering overall costs. But while the cost of implementing personalised cancer medicine may be high, what is the cost of not pursuing this course? ESMO recognises the need to develop and refine policy in these areas [34] and for considerable debate from all stakeholders.

The Specialty of Medical Oncology: Leading the Personalised Cancer Medicine Evolution

The convergence of clinical oncology, laboratory cancer research and molecular pathology is one of the most important factors driving the development of personalised cancer medicine [41]. But a well-recognised pit-fall of genomics-driven cancer medicine is the risk that large-scale genomic data generation could emerge without an evidence-based clinical approach to data analysis and interpretation [42].

While trying to optimise the therapeutic strategies for our patients by accelerating the incorporation of valuable data as soon as possible in practice, validation of both the diagnostic and therapeutic interventions is clearly needed before incorporating personalised cancer medicine into broad clinical practice. Considering the crucial implications of both false-positive or false-negative results for the patient, and the heterogeneity in testing methodology, the recent European Consensus Conference for external quality assessment in molecular pathology issued essential recommendations to ensure consistency of testing [25].

Emerging genomics need to be integrated into the existing spectrum of clinical knowledge and evaluated as part of a larger clinical context including age, performance status, disease burden, cancer cell lineage and histology. Although a major challenge, ESMO recognises that the medical oncology specialty has a central role to play in realising this personalised cancer medicine evolution.

As personalised cancer medicine transitions to the clinic, the concept of cancer as a systemic, highly heterogeneous and complex disease becomes even more apposite, and demands that quality cancer care should be provided by a multidisciplinary team (MDT) of highly qualified healthcare professionals, with medical oncologists at the core of the team. Medical oncologists act as the ‘patient interface’ within a multidisciplinary team [43] and carry a double duty: to raise awareness of the current achievements of targeted therapies, of their high potential (and limitations) and the

necessary requirements, and to guide their patients in seeking out clinical trials where their tumours can be better profiled, so that they can gain access to novel treatments.

Professional and Patient Education

Education for all stakeholders, including healthcare professionals, patients and their advocacy groups, biomedical researchers, the pharmaceutical and biotechnology industries, diagnostic and device industries, regulators, health economists and payers is essential to drive adoption of personalised cancer medicine. All stakeholders need access to timely, objective, authoritative and contextually interpreted information.

For physicians in training, medical schools are integrating genomic medicine into the curriculum, and postgraduate training programmes in translational genomics are now more common [44]. For oncologists already in post, providing effective training and support is an important objective [44]. ESMO recognises the challenges faced by practicing oncologists as genomic data and its interpretation continues to expand and change the established treatment paradigms in oncology. ESMO understands that it has a key role to play in providing this educational support and offers a full range of targeted information and education programmes that are continuously updated and further expanded to adequately reflect latest developments. This includes fellowships, CME certification and recertification programmes. ESMO will continue to provide validated diagnostic and treatment recommendations within its comprehensive set of more than 50 Clinical Practice Guidelines, updated on a regular basis [45], provide symposiums and support external conferences on targeted therapy and publish commentaries and opinion pieces relevant to personalised medicine [46]. ESMO has developed a range of e-learning resources for physicians, including a devoted area for e-learning on personalised medicine within its educational online portal OncologyPRO.

There are educational opportunities for patients on the ESMO website, including a guide to personalised medicine, which provides an overview on governing principles and examples of personalised medicine approaches in several tumour types, a video series explaining different aspects of personalised medicine and topic-specific sessions at the biannual ESMO Patient Seminar.

ESMO Future Outlook

For certain tumour types, the development of drugs against proteins coded by mutated cancer genes has revolutionised treatment and sent a disruptive wave rippling through medical oncology. Knowledge generation, its management and dissemination are expected to enable new interpretive processes and drive a new level of understanding regarding not only the treatment, but ultimately

the prevention of cancer. As the era of stratified oncology evolves into the era of personalised cancer medicine, driven in large part by the incredible speed of change in genomic technology, the potential to transform cancer care for our patients demands that the critical themes and questions raised in this statement form an ongoing dialogue with all stakeholders in oncology. This requires a new level of close collaboration with all disciplines. The specialty of medical oncology, operating at the centre of cancer care and the physician-patient interface, has the opportunity to act as enablers of the evolution and with the support of ESMO, shape the new personalised cancer medicine paradigm.

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